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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,488	02/16/2000	MAURICE MOLONEY	9369-98	6010

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BERESKIN AND PARR
SCOTIA PLAZA
40 KING STREET WEST-SUITE 4000 BOX 401
TORONTO, ON M5H 3Y2
CANADA

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,488	MOLONEY ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,12-16,18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,12-16,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 17, 2004 has been entered.

[2] Claims 1, 4-10, 12-16, and 18-19 are pending in the application.

[3] Applicant's amendment to the claims, filed March 03, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's arguments filed March 03, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

[6] Claims 4, 7, 9-10 and 13-14 are objected to in the recitation of "(c)". These claims depend from claim 1, which recites a step "c)", not "(c)". It is suggested that

applicants maintain consistency in the numbering of method steps. Appropriate correction is required.

[7] Claim 12 is objected to in the recitation of "gut or the of said animal". It is suggested that, for example, applicants amend the claim to recite "gut of said animal" (see for example claim 18).

Claim Rejections - 35 USC § 112, Second Paragraph

[8] In view of applicants' amendment to claim 8, the rejection under 35 USC 112, second paragraph, as set forth in item [9] of the Office action mailed September 17, 2003, is withdrawn.

[9] Claim(s) 1, 4-10, 12-16, and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 (claims 1, 4-10, 12-13, 15-16, and 18-19 dependent therefrom) and 14 are indefinite in the recitation of "pro-peptide". The specification defines the term "pro-peptide" as "the amino terminal portion of a zymogen or a functional portion thereof up to the maturation site" (page 5, bottom). The term is indefinite as it is unclear as to portion of a pro-peptide that is considered to be "functional". In the interest of advancing prosecution, the examiner has interpreted the term (in the context of claim 1) as meaning a portion (including a single amino acid) of a chymosin pro-peptide that allows cleavage of the fusion protein by an autocatalytically maturing aspartic protease.

Claim Rejections - 35 USC § 112, First Paragraph

[10] Claims 10 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claims 1 and 13, wherein the addition of the mature aspartic protease or chymosin in step c) takes place in vivo by transforming the host cell with an expression vector encoding the mature aspartic protease or chymosin and co-expressing the mature aspartic protease or chymosin in the host cell, does not reasonably provide enablement for the method of claims 1 and 13, wherein the mature aspartic protease or chymosin is added to the fusion protein under in vivo conditions by any means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP §

2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass the method of claims 1 and 13, wherein the mature aspartic protease or chymosin is added to the fusion protein under in vivo conditions by any means. In this case the disclosure is limited to for the method of claims 1 and 13, wherein the addition of the mature aspartic protease or chymosin in step c) takes place in vivo by transforming the host cell with an expression vector encoding the mature aspartic protease or chymosin and co-expressing the mature aspartic protease or chymosin in the host cell.

- The lack of guidance and working examples: While the specification fails to provide even a single working example of the claimed invention, i.e., practicing the methods under in vivo conditions, a skilled artisan would recognize that undue experimentation would not be required to practice the methods of claims 1 and 13, wherein the addition of the mature aspartic protease or chymosin in step c) takes place in vivo by transforming the host cell with an expression vector encoding the mature aspartic protease or chymosin and co-expressing the mature aspartic protease or chymosin in the host cell. However, the specification fails to provide guidance for practicing the methods of claims 1 and 13, wherein the mature aspartic protease or chymosin is added to the fusion protein under in vivo conditions by any means.

- The high degree of unpredictability in the art: In view of the lack of guidance and working examples, a skilled artisan would recognize that there is a high level of unpredictability in practicing the full scope of claimed methods.

- The amount of experimentation required is undue: While methods of cleaving a fusion protein in vitro are known, it is not routine in the art to identify all methods for cleaving a fusion protein by adding a mature aspartic protease or chymosin under in vivo conditions by any means. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It should be noted that, although the examiner has indicated enabled subject matter, this is no indication that such is supported by the instant specification, claims, and drawings as originally filed.

[11] Claims 12 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The lack of guidance and working examples: The specification fails to provide any guidance or a working example for practicing the claimed invention.

- The high degree of unpredictability in the art: In view of the complete lack of guidance and a working example, there is a high level of unpredictability in practicing the claimed invention.

- The amount of experimentation required is undue: As one of skill in the art must determine all aspects of the claimed method, particularly in view of the lack of guidance and working examples provided in the specification and the high degree of

unpredictability, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

It is noted that a scope of enablement rejection of claims 10, 12, 16, and 18 under 35 USC 112, first paragraph, has been raised and withdrawn in previous Office actions. However, upon further consideration of the claimed subject matter, the examiner has re-instated the rejection for those reasons stated above.

Claim Rejections - 35 USC § 102

[12] In view of applicants' cancellation of claims 20, 25, 26, 28-30, 41, 43, and 44, the rejection under 35 USC 102(b) as being anticipated by Hiramatsu et al. (Appl Environ Microbiol 56:2125-2132, 1990) as set forth in item [10] of the Office action mailed September 17, 2003, is withdrawn.

[13] Claim(s) 1, 4, 6-9, 13, 15, and 19 are rejected under 35 U.S.C. 102 (b) as being anticipated by Walsh et al. (J Biotech 45:235-241). The claims are drawn to a

method for the preparation of the recombinant protein comprising the following steps: transforming a host cell with an expression vector comprising: a transcription-regulating nucleic acid sequence, a chimeric nucleic acid sequence comprising a nucleic acid sequence encoding a chymosin pro-peptide linked in reading frame to a heterologous nucleic acid sequence encoding a recombinant polypeptide, immediately downstream of the pro-peptide-encoding sequence operatively linked to a nucleic acid encoding a functional termination region; growing the host cell to produce a fusion protein; and adding a mature form of an autocatalytically maturing aspartic protease capable of cleaving the chymosin pro-peptide to release the pro-peptide from the recombinant protein.

Walsh et al. teach an expression vector encoding a fusion protein having a linker comprising a Phe-Met chymosin cleavage site (page 237). Walsh et al. teach a method for producing the encoded fusion protein by transforming a host cell with the fusion expression vector, culturing the resulting transformant to express the protein, followed by cleavage of the fusion protein at pH 4 and 6.8 by addition of chymosin (page 236). This anticipates claims 1, 4, 6-9, 13, 15, and 19 as written.

It is noted that the instant rejection has been made based on the examiner's interpretation of the term "pro-peptide" as provided above (see item [9]). The specification indicates that the cleavage site of a bovine chymosin pro-peptide has the sequence Phe-Leu with Phe being the C-terminal amino acid of the bovine chymosin pro-peptide (page 19, top). As the chymosin cleavage site of the fusion protein of Walsh et al. comprises a Phe, which is considered by the examiner to be a "functional portion"

of a bovine chymosin pro-peptide, the cleavage site of the fusion protein of Walsh et al. has been recognized as a chymosin pro-peptide, in accordance with the definition provided in the specification (page 5, bottom).

Claim Rejections - 35 USC § 103

[14] The rejection of claims 1, 4, 6-10, 13-16, and 19 are under 35 U.S.C. 103(a) as being unpatentable over Hiramatsu et al. in view of Hiramatsu et al. as set forth in item [11] of the Office action mailed September 17, 2003, is withdrawn. It is noted that the instant rejection has not been withdrawn in view of applicants' arguments, but has instead been withdrawn in view of newly cited prior art.

[15] The rejection of claim 5 under 35 U.S.C. 103(a) as being unpatentable over Hiramatsu et al. in view of Hiramatsu et al. as applied to claims 1, 4, 6-10, 13-16, and 19 above and further in view of Fine et al. as set forth in item [12] of the Office action mailed September 17, 2003, is withdrawn. It is noted that the instant rejection has not been withdrawn in view of applicants' arguments, but has instead been withdrawn in view of the more relevant newly cited prior art (see item [16] below).

[16] Claim(s) 1, 4, 6-9, 13, 15, and 19 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Ward et al. (US Patent 6,265,204 B1) in view of McCaman et al. (J Biol Chem 261:15345-15348; cited in the IDS filed January 29, 2000). The claims are drawn to a method for the preparation of a recombinant protein as described above.

Ward et al. teach a nucleic acid encoding a fusion protein, wherein the nucleic acid encodes (from the 5'-end) a signal sequence, a secreted polypeptide, a cleavable

linker, wherein the cleavable linker is a chymosin prosequence, and two or more desired polypeptides (see particularly columns 7-8 and claim 17). Ward et al. teach that upon construction of the fusion nucleic acid, it is inserted into an expression vector comprising regulatory sequences that are functional in the host to be transformed, including transcriptional regulatory sequences and transcriptional start and stop sequences (column 11). Ward et al. teach that the fusion protein is produced by transforming an appropriate host cell with the fusion expression vector and culturing the transformant (column 13) followed by cleavage of the fusion protein (column 14). Ward et al. do not expressly teach the use of chymosin to cleave the produced fusion protein. However, at the time of the invention, one of ordinary skill in the art would have recognized that chymosin is an appropriate endoproteinase for cleaving a fusion protein comprising a chymosin prosequence. At the time of the invention, it was well known in the art that chymosin could autocatalytically cleave, i.e., self cleave, at the chymosin pro-propeptide-mature chymosin junction. Such is evidenced by McCaman et al. who teach that bovine prochymosin is autocatalytically activated by removal of the pro-sequence and that the prosequence is proteolytically cleaved at pH 4.5 (page 15345, left column).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Ward et al. and the state of art as represented by McCaman et al. for a method of producing and cleaving a fusion protein comprising a chymosin prosequence linker as taught by Ward et al. using chymosin as a cleaving agent optionally at a pH of 4.5. One would have been motivated for a method of cleaving a

fusion protein comprising a chymosin prosequence linker as taught by Ward et al. using chymosin as a cleaving agent optionally at a pH of 4.5 because it was well known in the art at the time of the invention that chymosin can cleave its propeptide at a pH of 4.5. One would have a reasonable expectation of success for a method of cleaving a fusion protein comprising a chymosin prosequence linker as taught by Ward et al. using chymosin as a cleaving agent optionally at a pH of 4.5 because of the results of Ward et al. and the state of the art at the time of the invention. Therefore, claims 1, 4, 6-9, 13, 15, and 19, drawn to the methods as described above would have been obvious to one of ordinary skill in the art.

[17] Claim(s) 5 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Ward et al. in view of McCaman et al. as applied to claims 1, 4, 6-9, 13, 15, and 19 above and further in view of Fine et al. (*Gen Comp Endocrinol* 89:51-61; cited in the Office action mailed December 04, 2001). Claim 5 limits the recombinant protein to hirudin or carp growth hormone.

Ward et al. and McCaman et al. disclose the teachings as described above. Additionally, Ward et al. teach that their method can be used to express a fusion protein comprising an epitope for affinity purification of the fusion protein (see column 10, top). Neither Ward et al. nor McCaman teach a method for producing a recombinant carp growth hormone.

Fine et al. teach the recombinant expression of carp growth hormone (cGH) using Escherichia coli as an expression host (page 52, right column). Fine et al. teach

the cDNA sequence of cGH has been isolated and characterized (page 52, left column, bottom to right column, top).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Ward et al., McCaman et al., and Fine et al. for a method for producing cGH by recombinantly expressing cGH fused to an affinity epitope with a chymosin prosequence linker and cleaving said fusion protein using chymosin as a cleaving agent. One would have been motivated to practice the method of Ward et al. with cGH as a desired protein in order that: 1) the cGH protein is expressed by a eukaryotic cell and 2) the cell secretes the protein into the culture medium thereby reducing purification steps and time. One would have been motivated to express cGH with an affinity epitope in order to allow affinity purification of the protein. One would have a reasonable expectation of success for a method of producing and cleaving a fusion protein comprising cGH and an affinity tag as a desired recombinant protein and a chymosin prosequence linker as taught by Ward et al. using chymosin as a cleaving agent because of the results of Ward et al., the state of the art at the time of the invention as represented by McCaman et al. and Fine et al. Therefore, claim 5, drawn to the method as described above would have been obvious to one of ordinary skill in the art.

[18] Claim(s) 5 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Walsh et al. in view of Fine et al. Claim 5 limits the recombinant protein to hirudin or carp growth hormone.

Walsh et al. and Fine et al. disclose the teachings as described above. Additionally, Walsh et al. teach that their method can be used to express a fusion protein comprising an affinity tail fused to the protein of interest to facilitate purification (page 235). Walsh et al. do not teach a method for producing a recombinant carp growth hormone.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Walsh et al. and Fine et al. for a method for producing cGH by recombinantly expressing cGH fused to an affinity tail with a chymosin prosequence linker and cleaving said fusion protein using chymosin as a cleaving agent. One would have been motivated to practice the method of Walsh et al. to recombinantly produce cGH with an affinity tail followed by cleavage of the affinity tail in order to facilitate purification as described above. One would have a reasonable expectation of success for a method of producing and cleaving a fusion protein comprising cGH and an affinity tag as a desired recombinant protein and a chymosin prosequence linker as taught by Walsh et al. using chymosin as a cleaving agent because of the results of Walsh et al. and Fine et al. Therefore, claim 5, drawn to the method as described above would have been obvious to one of ordinary skill in the art.

[19] Claim(s) 14 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Walsh et al. in view of Dunn et al. ("Aspartic Proteinases", Advances in Experimental Medicine and Biology, Volume 362, Plenum Press, NY, 1995, pages 1-9) OR Ward et al. in view of McCaman et al. as applied to claims 1, 4, 6-9, 13, 15, and 19

above and further in view of Dunn et al. Claim 14 limits the aspartic protease added in step c) to an aspartic protease that is heterologous to the chymosin pro-peptide.

Walsh et al., Ward et al., and McCaman et al. disclose the teachings as described above. Neither Walsh et al., Ward et al., nor McCaman et al. teach cleavage of a chymosin pro-peptide using a heterologous aspartic protease.

Also, at the time of the invention, it was well known in the art that aspartic proteases could cleave heterologous pro-peptides. For example, Dunn et al. teach that a plurality of aspartic proteases have the ability to proteolytically cleave a recognition site having Phe in the P1 position (page 5). Thus, one of ordinary skill in the art would have recognized that the cleavage sites as taught by Ward et al. and Walsh et al., which have Phe at the P1 position, would have been cleaved by other aspartic proteases as well. Moreover, applicants have acknowledged that a skilled artisan would "display the same characteristics with respect to structure, enzyme activation, and the catalytic mechanism of peptide cleavage" and that "[a]s a result, we submit that one of skill in the art would readily expect that a pro-peptide from any aspartic protease would be useful in the present invention" (see pages 5-6 of the response filed February 04, 2003).

Also, at the time of the invention, it was well known in the art that aspartic proteases exhibited non-specific cleavage.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Walsh et al., Ward et al., McCaman et al., and Dunn et al. for a method of producing and cleaving a fusion protein comprising a chymosin pro-propeptide using an aspartic protease other than chymosin as a cleaving agent. One

would have been motivated for a method of producing and cleaving a fusion protein comprising a chymosin pro-propeptide using an aspartic protease other than chymosin as a cleaving agent in order to identify an aspartic protease that cleaves the fusion protein with a lower occurrence of non-specific cleavage of the desired protein. One would have a reasonable expectation of success for a method of producing and cleaving a fusion protein comprising a chymosin pro-propeptide using an aspartic protease other than chymosin as a cleaving agent because of the results of Walsh et al., Ward et al., McCaman et al., and Dunn et al. Therefore, claim 14, drawn to the method as described above would have been obvious to one of ordinary skill in the art.

[20] Response to argument: Applicant traverses the instant rejection (beginning at page 6 of the response) by arguing that the novelty of the claimed invention is supported by the Protein Engineering reference (although not expressly stated, it appears applicants are referring to Kuhnel et al. Prot Engineer 16:777-783), which is a peer-reviewed journal. Applicants' argument is not found persuasive.

The examiner does not dispute applicants' assertion that the reference of Kuhnel et al. has undergone a peer-review process prior to publication. However, a peer-review process and/or publication in a technical journal does not exclude a claimed invention from the novelty requirements of 35 USC 102 and 103.

Applicants argue that even if one of ordinary skill in the art would have been motivated to add the mature form an aspartic protease such as chymosin, there is no reasonable expectation of success for the following reasons: 1) one of ordinary skill in the art would have used the chymosin's substrate cleavage site (Phe-Met) instead of a

chymosin pro-peptide cleavage site (citing the reference of Walsh et al. J Biotech 45:235-241); 2) proteases exhibit non-specific cleavage; 3) protease cleavage may result in "foreign" amino acids attached to the protein of interest; 4) proteases exhibit inefficient or incomplete cleavage; and 5) there is a long-felt need for the present invention. Applicants' argument is not found persuasive.

Regarding argument 1), it is noted that the prior art recognizes that pro-chymosin is converted to chymosin in part by autocatalytic cleavage, i.e., self cleavage, at the pro-peptide junction to yield mature chymosin. Thus, one of ordinary skill in the art at the time of the invention would have recognized that chymosin has the ability to cleave the peptide bond joining the pro-peptide to the mature form of chymosin and that the junction of the pro-peptide of chymosin is a natural chymosin substrate.

Addressing arguments 2), 3), and 4), there is no dispute that proteases often exhibit non-specific cleavage, incomplete cleavage, i.e., not all amino acid sequences comprising a protease cleavage site will be cleaved in the presence of the cognate protease, and that cleavage of a fusion protein may result in heterologous amino acids fused to the desired protein. However, it is noted that applicants' arguments are not commensurate in scope with the claims. An inspection of the claims reveals that there is no limitation that requires no non-specific and incomplete cleavage occur and that no cleavage resulting in heterologous amino acids fused to the recombinant protein occur. See MPEP 2145 regarding arguing limitations that are not claimed.

Addressing argument 5), it is noted that MPEP 2141 acknowledges that long felt need "might be utilized to give light to the circumstances surrounding the origin of the

subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquires may have relevancy." However, in view of the prior art as cited above, one of ordinary skill in the art would have recognized that even if such a long felt need existed at the time of the invention, this need has already been satisfied.

Conclusion

[21] Status of the claims:

- Claims 1, 4-10, 12-16, and 18-19 are pending.
- Claims 1, 4-10, 12-16, and 18-19 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman
Patent Examiner
Art Unit 1652
04-28-04